Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 253–259

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Outcome of patients with recurrent adult-type granulosa cell tumors – A Taiwanese Gynecologic Oncology Group study

Peng-Hui Wang [a, b, c], Hsu-Dong Sun [b, d], Hao Lin [e], Kung-Liahng Wang [f], Wen-Shiung Liou [g], Yao-Ching Hung [h], Ying-Cheng Chiang [i], Chien-Hsing Lu [b, j], Hung-Cheng Lai [k], Ting-Chang Chang [l, *], Taiwanese Gynecologic Oncology Group[1]

[a] Division of Gynecology, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, National Yang-Ming University School of Medicine, Taipei, Taiwan
[c] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[d] Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, Ban Ciao, New Taipei City, Taiwan
[e] Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[f] Department of Obstetrics and Gynecology, Mackay Memorial Hospital and Mackay Medical College, Taipei, Taiwan
[g] Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[h] Department of Obstetrics and Gynecology, College of Medicine, China Medical University and China Medical University Hospital, Taichung, Taiwan
[i] Department of Obstetrics and Gynecology, National Taiwan University and National Taiwan University Hospital, Taipei, Taiwan
[j] Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung, Taiwan
[k] Department of Obstetrics and Gynecology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan
[l] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Accepted 9 December 2014

Keywords:
ovarian granulosa cell tumor
recurrent granulosa cell tumor
recurrent ovarian neoplasm
adult granulosa cell tumor
survival outcome
Taiwanese Gynecologic Oncology Group

ABSTRACT

Objective: The aim of this study is to evaluate the long-term outcome of ovarian recurrent granulosa cell tumors (GCTs) in a large series of patients treated in Taiwanese Gynecologic Oncology Group (TGOG) centers and to define the prognostic parameters for survival.
Materials and methods: A retrospective multi-institutional review of patients with recurrent ovarian GCTs treated in TGOG centers was conducted. The clinical and pathological characteristics, treatment, and outcomes of patients with ovarian recurrent GCTs were analyzed using Kaplan-Meier and Cox proportional hazards analyses to determine the predictors for survival.
Results: A total of 44 patients from 16 medical centers were identified between January 1994 and December 2010. The median disease-free survival (DFS), postrecurrence survival, and overall survival (OS) were 61.5 months (range, 3.7–219.3 months), 55.8 months (range, 4.6–193.7 months), and 115.3 months (range, 17.2–390.6 months), respectively. In multivariate analysis, DFS (> 61.5 months versus ≤ 61.5 months, hazard ratio (HR) 0.15, 95% confidence interval (CI) 0.03–0.78, $p = 0.024$) at the initial operation after diagnosis of relapse was the only predictor that correlated with OS.
Conclusion: DFS after the initial operation was the only important predictor for overall survival in patients with recurrent GCTs, regardless of treatment, suggesting that the natural behavior of the tumor is a critical factor for patients with recurrent GCTs.

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University, 5 Fu-Shin Street, Kueishan, Taoyuan 333, Taiwan. Tel.: +886 3 328 1200; fax: +886 3 328 8252.
E-mail addresses: tinchang@cgmh.org.tw, tinchang.chang@gmail.com (T.-C. Chang).

[1] Taiwanese Gynecologic Oncology Group comprised the directors and representing authors in every medical center, contributing to the study for all gynecology-related tumors, and included Ming-Shyen Yen (Taipei Veterans General Hospital), Chi-An Chen (National Taiwan University Hospital), Chyong-Hyeu Lai (Chang Gung Memorial Hospital), Mu-Shyen Yu (Tri-Service General Hospital), Cheng-Yang Chou (National Cheng Kung University), Chi-Lun Chang (Mackay Memorial Hospital), Dr. Kuo-Feng Huang (Chi-Mei Foundation Medical Hospital), Chih-Ming Ho (Cathay General Hospital), Tan-Yuan Chu (Tzu Chi University), Po-Hui Wang (Chung Shan Medical University Hospital), Fu-Shing Liu (Show Chwan Memorial Hospital), Yuen-Yee Kan (Kaohsiung Yuan Hospital), Ching-Hu Wu (Kaohsiung Medical University), and others.

http://dx.doi.org/10.1016/j.tjog.2014.12.007

Introduction

Ovarian adult-type granulosa cell tumors (GCTs) are derived from ovarian sex-cord stromal hormone-secreting tumors; they are rare and characterized as having slow, indolent growth, and late-recurrence [1–3]. The prognostic factors for GCTs include older age, advanced stage (Stage II–IV), large tumor size, high mitotic index, tumor rupture, and the presence of residual tumor after initial surgery [4–21]. These prognostic factors are frequently identified with tumor recurrence, not survival, after the initial treatment of primary GCTs. Due to the above-mentioned characteristics of GCTs, it is difficult to obtain data on long-term follow-up of a large number of patients. The treatment and outcome of recurrent GCTs is still uncertain. Only a few reports are available in the literature and the number of participants in these studies was small [22–28]. The current study was conducted from 16 medical centers in Taiwan to investigate the outcomes of patients with recurrent GCTs.

Materials and methods

This was a subsequent study of the original design from the Taiwanese Gynecologic Oncology Group (TGOG) study [5,6] to investigate the outcome of patients with GCTs (TGOG-3001A) [5], based on 16 medical centers in Taiwan [5,6]. All GCTs were confirmed by central pathological review. The study period was between January 1994 and December 2010 and only patients with recurrent GCTs were included (TGOG-3001B). Approval for this study was obtained from the institutional review boards of all medical centers involved. Part of the data (36 patients) have previously been published [5]. Patient characteristics included clinical and pathological parameters, and treatment for either primary or recurrent tumors. Data collection included records of the initial operation for the primary tumors (GCTs) and secondary treatment for the recurrent GCTs. Disease-free survival (DFS) was calculated from the date of the initial operation for the primary GCTs to the date of relapse. Postrecurrent survival was calculated from the date of the diagnosis of relapse to the date of death or the date of the last follow-up, and overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of the last follow-up. To determine an appropriate decision point for the continuous data, such as age, body mass index (BMI), tumor size, DFS, and post-recurrent survival, the receiver operating characteristic was used [29]. Statistical analysis was conducted using SPSS version 18 (SPSS, Inc., Chicago, Il, USA). A p value < 0.05 was defined as statistically significant; all tests were 2-tailed. The recurrence curves were calculated using the Kaplan-Meier method, and the log-rank test was used to compare the recurrence curves. Univariate and multivariate analyses were performed using the Cox regression model, and Pearson's Chi-square test and Fisher's exact test were used to compare the differences in proportions.

Results

A total of 44 patients had recurrent GCTs. At initial diagnosis, most patients were multipara (79.5%), symptomatic (84.1%), at an early stage (Stage I: 79.5%), and treated with exploratory laparotomy (81.8%) and incomplete staging surgery (63.5%), and were without adjuvant chemotherapy ($n = 30$, 68.2%). The most common chemotherapy regimen was bleomycin, etoposide, and cisplatin (BEP) regimen (13/44). The median OS was 111.2 months, ranging from 17.2 months to 390.6 months for all patients, and 115.3 months, ranging from 17.2 months to 390.6 months, when one patient who died of lung cancer was excluded. The median DFS was 61.5 months, ranging from 3.7 months to 219.3 months (Table 1).

Table 1
Patient and tumor characteristics at initial diagnosis ($n = 44$).

Characteristic	
Age (y)	44 (20–73)
Nullipara	9 (20.5)
Multipara	35 (79.5)
Premenopause	27 (61.4)
Postmenopause	17 (38.6)
Body mass index	23.1 (16.0–32.9)
Associated medical illness[a]	
Hypertension	9 (20.5)
Diabetes mellitus	7 (15.9)
Others	5 (11.4)
Thyroid	2 (4.5)
Depression	1 (2.3)
Stroke	1 (2.3)
Systemic lupus erythematous	1 (2.3)
Associated with medical illness	
Yes	14 (31.8)
History of previous hysterectomy	
Yes	2 (4.5)
Symptoms	
Abdominal pain and fullness	17 (38.6)
Abdominal mass	8 (18.2)
Abnormal bleeding	18 (40.9)
Symptoms	
Yes	37 (84.1)
Stage	
IA	22 (50.0)
IC	13 (29.5)
IIIA	1 (2.3)
IIIC	6 (13.6)
IV	2 (4.5)
Stage	
≤ I	35 (79.5)
> I	9 (20.5)
Tumor size (cm)	12 (1–35)
Bilaterality	
Yes	20 (45.5)
Laparoscopy	8 (18.2)
Exploratory laparotomy	36 (81.8)
USO	20 (45.5)
BSO and TH	8 (18.2)
Complete staging surgery	16 (36.4)
Residual tumor	
Yes	7 (15.9)
Adjuvant chemotherapy	
Yes	14 (31.8)
Chemotherapy regimen	
BEP	13 (29.5)
VAC	1 (2.3)
Chemotherapy cycles	
0	30 (68.2)
1	1 (2.3)
3	7 (15.9)
4	2 (4.5)
6	4 (9.1)
Chemotherapy cycles	
1–3	8 (18.2)
> 3	6 (13.6)
Disease-free survival (mo)	61.5 (3.7–219.3)
Overall survival (mo)	111.2 (17.2–390.6)
Disease-free survival (mo)[b]	62.1 (3.7–219.3)
Overall survival (mo)[b]	115.3 (17.2–390.6)

Data are presented as median (range) or n (%).
BEP = bleomycin, etoposide, cisplatin; BSO = bilateral salpingo-oophorectomy; TH = total hysterectomy; USO = unilateral salpingo-oophorectomy; VAC = vinblastine, adriamycin, and cisplatin.
[a] Some patients had more than one medical disease.
[b] One patient died from lung cancer and was excluded from this analysis.

Most patients had peritoneal recurrence (88.6%), but did not have symptoms (61.4%); therefore, these symptomless patients were found accidentally during the follow-up. These recurrent patients were mainly treated with surgery-based therapy (77.3%), including nine patients (20.5%) with surgery alone and the

remaining with surgery and postoperative adjuvant therapy, such as chemotherapy and radiation. Up to two-thirds of patients (65.9%) were treated with various kinds of chemotherapies, the most frequent regimen of chemotherapy was BEP. If the patients had been treated with a BEP regimen, bleomycin was avoided and only a combination of etoposide and cisplatin was used. During the follow-up, 14 patients died: 13 deaths were disease-related and one patient died of lung cancer. The overall mortality rate of the patients with recurrent GCTs was 31.8% (14/44) and 30.3% (13/43), respectively. The median postrecurrent survival was 55.8 months, ranging from 4.6 months to 193.7 months (Table 2).

In terms of prognostic factors at the initial diagnosis, univariate analysis showed that only BMI and DFS were correlated with OS. However, DFS alone contributed to OS in recurrent patients. If the patients had a DFS of > 61.5 months, the risk of disease-related death was significantly decreased [hazard ratio (HR), 0.15, 95% confidence interval (CI), 0.03–0.78; $p = 0.024$] (Table 3).

The characteristics of patients when they were diagnosed as having recurrence was also analyzed (Table 4). Only post-recurrence survival contributed to OS in these recurrent patients. If the patients had postrecurrence survival of > 51.8 months after secondary treatment for recurrent tumors, the risk of disease-related death significantly decreased (HR, 0.10; 95% CI, 0.02–0.53; $p = 0.007$), suggesting that complete resection for a recurrent tumor might provide a better opportunity of survival for patients with recurrent GCTs.

Table 2
Patient and tumor characteristics at recurrence ($n = 44$).

Characteristic	
Age (y)	50.1 (22–75)
Symptoms	
Yes	17 (38.6)
Asymptomatic	27 (61.4)
Metastatic site	
Peritoneal cavity (upper and low)	39 (88.6)
Liver parenchyma	6 (13.6)
Lymph node	4 (9.1)
Bone	1 (2.3)
Treatment	
Nil	2 (4.5)
Surgery alone	9 (20.5)
Chemotherapy alone	8 (18.2)
Surgery and chemotherapy	23 (52.3)
Surgery and concurrent chemoradiation	2 (4.5)
Surgery-based therapy	
Yes	34 (77.3)
No	10 (22.7)
Chemotherapy regimen	
Nil	12 (27.3)
BEP	21 (47.7)
EP	3 (6.8)
PC	5 (11.4)
Paclitaxel	1 (2.3)
Cisplatin	2 (4.5)
Chemotherapy regimen	
Single (paclitaxel or cisplatin)	3 (6.8)
Combination (BEP or EP or PC)	29 (65.9)
Chemotherapy regimen	
BEP or EP	24 (54.5)
PC or paclitaxel	6 (13.6)
Cisplatin	2 (4.5)
Cycles of chemotherapy	
1–3	10 (22.7)
> 3	22 (50.0)
Overall survival rate	
Death	14 (31.8); 13 (30.3)[a]
Alive	30 (68.2); 30 (69.7)[a]
Postrecurrence survival (mo)[a]	55.8 (4.6–193.7)

Data are presented as median (range) or n (%).
BEP = bleomycin, etoposide, cisplatin; EP = etoposide and cisplatin; PC = paclitaxel and cisplatin.
[a] One patient died from lung cancer and was excluded from this analysis.

Discussion

The typical clinical scenario of patients with GCTs is usually a middle-aged female presenting with a pelvic mass or endocrine syndrome due to a functional tumor, especially estrogen secretion [30,31]. This was consistent with the findings in the current study patients at the initial operation, since symptoms, such as abdominal pain, pelvic mass, and irregular bleeding occurred in most patients (> 80%). However, < 40% of recurrent patients presented symptoms; that is to say, > 60% of patients were identified at the routine postoperative follow-up and were detected accidentally.

In contrast to epithelial ovarian cancer, GCTs are characterized by slow, indolent growth with a tendency toward later recurrence [30], As much as 70–90% of GCTs were diagnosed at Stage I [26], and in a TJOG study with a large sample size ($n = 176$), nearly 80% of patients were at Stage I [5]. Low staging at the initial operation confers an excellent prognosis, with a 5-year OS rate reported to be 75–96.5%, and a 10-year OS rate reported as 94.1% [5]. However, the OS rates dropped to 55–75% and 22–50% for Stages II and III/IV, respectively [31]. In this study, nine patients were in an advanced stage (9/44, 20.5%), and most patients were Stage I (79.5%), which was very close to the above-mentioned original stage of the patients at the initial operation [5].

The median time from the initial operation to the detection of recurrence was 61.5 months, ranging from 3.7 months to 219.3 months (Table 1). In agreement with previous reports, frequent sites of recurrence included the upper abdomen (55–70%) and pelvis (30–45%) [2,23,26–28,31]. In this study, recurrence at the abdominal cavity was most common (88.6%). With respect to the sites of recurrence of primary and recurrent GCTs, Fotopoulou et al [23] showed in a recent evaluation that tumor dissemination pathways followed by primary and recurrent GCTs differed significantly, based on the higher rates of multivisceral tumor involvement in disease recurrence. They found that a primary presentation of extrapelvic involvement with peritoneal carcinomatosis was rare. Lee et al [26] also showed that the most common sites of recurrence were the pelvic cavity, followed by the liver and the intestine, but the vast majority of the recurrent cases presented with extrapelvic metastases. In this study, more than two-thirds of the patients with intraperitoneal recurrence had upper abdomen involvement. In addition, 23.3% of patients had multi-organ involvement.

In terms of nodal involvement in patients with recurrent GCTs, Brown et al [32], in an attempt to describe the incidence of nodal involvement in patients with recurrent GCTs, could show that only six (5.1%) out of a total of 117 patients whose disease eventually recurred had nodal metastases at the time of recurrence. In fact, three of these six patients had negative lymph nodes at initial staging [32]. Consistent with the rarity of nodal involvement in GCTs at both the initial operation and also in recurrence, just six patients (13.6%) had recurrence on the lymph nodes in this study.

The concept of the management of recurrent GCTs is still controversial. Similar to epithelial ovarian cancers, intraperitoneal recurrence of GCTs is most common. Therefore, in contrast to the clear role of adjuvant chemotherapy in recurrent epithelial ovarian cancer, the surgery for recurrent GCTs might be a better alternative [28], due to the characteristically slow, indolent pattern of progression, even for recurrent GCTs. The value of surgery is mainly based on the initial operation for GCTs. For example, in a comparison of the outcomes of patients with GCTs before and after 1988, Hölscher et al [11] found significant improvements in 5-year and 10-year OS, from 55.8% to 89.1% and from 42.8% to 85.2%, respectively.

Table 3
Univariate and multivariate Cox regression analyses at the initial diagnosis ($n = 43$).

Characteristics	No.	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age					
≤ 45	24	1 (Ref)		1 (Ref)	
> 45	19	2.100 (0.681–6.471)	0.196	1.877 (0.382–9.221)	0.438
Nullipara					
No	34	1 (Ref)			
Yes	9	0.687 (0.151–3.117)	0.627		
Menopause					
No	27	1 (Ref)			
Yes	16	2.585 (0.840–7.956)	0.098		
Body mass index					
≤ 23.6	25	1 (Ref)		1 (Ref)	
> 23.6	18	3.684 (1.109–12.237)	0.033	2.839 (0.666–12.097)	0.158
Associated with medical illness					
No	30	1 (Ref)			
Yes	13	0.891 (0.273–2.904)	0.848		
History of hysterectomy					
No	42	1 (Ref)			
Yes	1	0.048 (0.000–2.156E7)	0.765		
Symptoms					
No	7	1 (Ref)			
Yes	36	0.570 (0.150–2.169)	0.410		
Stage					
IA	22	1 (Ref)			
IC	12	5.048 (1.194–21.350)	0.028		
IIIA	1	0.000	0.991		
IIIC	6	4.432 (0.700–28.047)	0.114		
IV	2	6.354 (1.015–39.770)	0.048		
Stage					
≤ I	34	1 (Ref)		1 (Ref)	
> I	9	2.221 (0.682–7.235)	0.185	2.280 (0.402–12.922)	0.352
Bilaterality					
No	24	1 (Ref)			
Yes	19	2.635 (0.847–8.201)	0.094		
Tumor size (cm)					
≤ 11.5	21	1 (Ref)			
> 11.5	22	0.654 (0.214–1.994)	0.455		
Laparoscopy					
No	35	1 (Ref)			
Yes	8	1.760 (0.483–6.416)	0.392		
Complete staging surgery					
No	28	1 (Ref)			
Yes	15	2.207 (0.731–6.661)	0.160		
Residual tumor					
No	36	1 (Ref)			
Yes	7	1.904 (0.522–6.941)	0.329		
Adjuvant chemotherapy					
No	29	1 (Ref)		1 (Ref)	
Yes	14	2.128 (0.713–6.354)	0.176	1.348 (0.313–5.811)	0.688
Chemotherapy regimen					
Nil	29	1 (Ref)			
BEP	13	1.807 (0.572–5.713)	0.313		
VAC	1	51.074 (3.049–855.455)	0.006		
Chemotherapy cycles					
0	29	1 (Ref)			
1–3	8	1.475 (0.378–5.762)	0.576		
> 3	6	3.797 (0.946–15.234)	0.060		
Disease-free survival (mo)[a]					
≤ 61.5	21	1 (Ref)		1 (Ref)	
> 61.5	22	0.201 (0.054–0.753)	0.017	0.150 (0.029-0.779)	0.024

BEP = bleomycin, etoposide, cisplatin; HR = hazard ratio; VAC = vinblastine, adriamycin, and cisplatin.
[a] One patient died from lung cancer and was excluded from this analysis.

The authors proposed that these improvements in survival may be attributed partly to advances in treatment, such as improved surgery without residual tumors, and finally concluded that surgery remains the cornerstone of treatment. In addition, many studies showed favorable outcomes for GCTs after complete excision, without residual tumor at the initial operation [2,5,7,9,11,26].

With respect to surgical experience with recurrent disease, data are far more limited. Fotopoulou et al [23] used a multivisceral operative approach, including extensive peritonectomy, intestinal or diaphragmatic resection, splenectomy, and partial hepatectomy/pancreatectomy, and found that 85.2% of recurrent patients could be operated on tumor-free. This concept was also supported by a study from Korea, where > 80% of recurrent patients could be optimally debulked during the second operation [26]. In a much smaller study, Chua et al [22] reported prolonged survival following a maximal cytoreductive effort for

Table 4
Univariate and multivariate Cox regression analyses after recurrence ($n = 43$).

Characteristics	No.[a]	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age (y)					
≤ 52	24	1 (Ref)		1 (Ref)	
> 52	19	2.317 (0.706–7.608)	0.166	2.063 (0.582–7.314)	0.262
Symptoms					
No	27	1 (Ref)			
Yes	16	1.541 (0.515–4.606)	0.439		
Only peritoneal invasion					
No	5	1 (Ref)			
Yes	38	1.033 (0.223–4.782)	0.967		
Metastasis to > 1 organ					
No	33	1 (Ref)		1 (Ref)	
Yes	10	3.311 (0.922–11.889)	0.066	0.954 (0.223–4.083)	0.949
Treatment					
Surgery alone	9	0.374 (0.048–2.925)			
Others	34	1 (Ref)	0.349		
Treatment					
Chemotherapy alone	8	0.516 (0.111–2.396)			
Others	35	1 (Ref)	0.398		
Surgery-based therapy					
No	9	1 (Ref)			
Yes	34	1.160 (0.310–4.341)	0.825		
Adjuvant chemotherapy					
No	11	1 (Ref)		1 (Ref)	
Yes	32	1.709 (0.377–7.740)	0.487	1.386 (0.291–6.613)	0.682
Chemotherapy regimen					
Nil	11	1 (Ref)			
BEP	21	1.568 (0.325–7.578)	0.576		
EP	3	9.554 (1.212–75.303)	0.032		
PC	5	1.743 (0.244–12.451)	0.580		
Paclitaxel	1	0.000	0.990		
Cisplatin	2	0.000	0.994		
Chemotherapy regimen					
Nil	11	1 (Ref)			
Single (paclitaxel or cisplatin)	3	0.000	0.985		
Combination (BEP or EP or PC)	29	1.901 (0.420–8.602)	0.404		
Chemotherapy regimen					
Nil	11	1 (Ref)			
BEP or EP	24	1.939 (0.418–8.995)	0.398		
PC or paclitaxel	6	1.257 (0.175–9.052)	0.820		
Cisplatin	2	0.000	0.987		
Chemotherapy cycles					
0	11	1 (Ref)			
1–3	10	2.859 (0.571–14.316)	0.201		
> 3	22	1.166 (0.226–6.018)	0.855		
Postrecurrence survival (mo)					
≤ 51.8	20	1 (Ref)		1 (Ref)	
> 51.8	23	0.086 (0.020–0.368)	0.001	0.101 (0.019–0.529)	0.007

BEP = bleomycin, etoposide, cisplatin; EP = etoposide and cisplatin; PC = paclitaxel and cisplatin.
[a] One patient died of lung cancer and was excluded from this analysis.

peritoneal metastases from recurrent GCTs, as all five patients were still alive 10–95 months after treatment, with no evidence of disease. Although Fotopoulou's group [23] and Lee's group [26] both showed a very high rate (> 80%) of successful cytoreduction (optimally debulking surgery) in these recurrent-GCT patients with multifocal lesions, there was no doubt that surgical cytoreduction during relapse is more challenging and involves a multivisceral approach [23]. In fact, Uygun's group [27] found that only two of 11 patients could undergo surgical tumor debulking. In the current study, up to 80% of patients were initially treated with surgery for recurrent tumors, and among this group, one-quarter of the recurrent CGTs (26.5%, 9/34) were treated with surgery alone (20.5% of all recurrent patients, Table 2). Both treatment approaches contributed to the acceptable outcome, since more than two-thirds (68.2% or 69.7%) of recurrent patients were still alive after secondary treatment. Although surgery alone or surgery-based therapy seemed not to have a statistically significant effect on OS (Table 4), it appears that complete resection of a recurrent tumor might provide the best opportunity for patient survival.

In terms of adjuvant therapy, such as chemotherapy, radiation, or others, there is an absence of agreement on the best and most favorable regimen for recurrent GCTs, although BEP might be one of the best choices, based on the relatively better response rate, ranging from 51% to 90% at the advanced-stage or in recurrent patients [22,33–35]. However, the effectiveness of this treatment remains poor, with a median DFS of only 14–24 months [33–35]. In this study, > 80% of the patients had been treated with BEP therapy, either at the initial operation or at recurrence. One patient was treated with a vinblastine, Adriamycin, and cisplatin (VAC) regimen at the initial operation, five patients were treated with paclitaxel and cisplatin, two patients with single-agent cisplatin, and one patient with paclitaxel. The role of paclitaxel in the treatment of GCTs is still uncertain, although one report concluded that

paclitaxel demonstrated activity against sex cord-stromal tumors of the ovary and may be less toxic than BEP, and suggested that combined paclitaxel and platinum chemotherapy warrants further investigation [36]. However, in this study, neither the chemotherapy regimens nor the cycles of chemotherapy ($\leq$ 3 cycles versus > 3 cycles) made a statistically significant contribution to OS either at the initial operation or when treating recurrence (Tables 3 and 4). With regard to radiation or other therapies, such as hormonal therapies and antivascular agent therapies, that have been reported in the literature [22,25,37–41], the response rate was 43% (6/14) in a radiation group [37] and 40% (2/5) in a leuprolide acetate treatment group [38], respectively. However, these reports might be considered as personal experiences [25,39–41].

There are some limitations in the current study. Firstly, this was a multicenter, retrospective study, so the selection bias inherent to this kind of design may have been introduced into the study. Although the best way to avoid or minimize this bias is to conduct a prospective randomized study, this was not feasible due to the characteristics of GCTs, including their rarity, slow and indolent growth, and late recurrence. A retrospective study with a large data set is still the accepted way to investigate this kind of problem. Secondly, the patient sample size in this study was relatively small. Despite these limitations, the data presented here is still useful, since it may be the first attempt and largest series to report outcomes among a Taiwanese population (in Taiwan).

Conclusion

From the study findings, surgery-based therapy could be considered as the primary choice for patients with recurrent GCTs, since the vast majority of recurrent tumors involve the abdominal cavity, maximal cytoreduction with a curative intent via a multivisceral operative approach for these patients could be attempted at first. In addition, it was found that the tumor behavior of GCTs might be one of the most important critical factors impacting prognosis, as DFS at the initial operation (> 61.5 months) was the only contributor to OS in recurrent GCT patients.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported in part by grants from the National Science Council of Taiwan (NSC 99–2314–B–010–009–MY3 and NSC 102–2314–B–010–032) and Taipei Veterans General Hospital (V101C1–128; V102C–141; V101E5–006; V102E4–003; V103A–016; V103C–112; and V103E4–003).

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study. We thank Wen-Hsun Chang, BS, MPH, for her valuable participation in data management and analyses. We also thank the Medical Science & Technology Building of Taipei Veterans General Hospital for providing experimental space and facilities.

References

[1] Geetha P, Nair MK. Granulosa cell tumours of the ovary. Aust N Z J Obstet Gynaecol 2010;50:216–20.
[2] Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. J Clin Oncol 2007;25:2944–51.
[3] Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol 2003;21:1180–9.
[4] Oztekin D, Kurt S, Camuzcuoglu H, Balsak D, Dicle N, Tinar S. Granulosa cell tumors of the ovary: Review of 43 cases. J BUON 2012;17:461–4.
[5] Sun HD, Lin H, Jao MS, Wang KL, Liou WS, Hung YC, et al. A long-term follow-up study of 176 cases with adult-type ovarian granulosa cell tumors. Gynecol Oncol 2012;124:244–9.
[6] Weng CS, Chen MY, Wang TY, Tsai HW, Hung YC, Yu KJ, et al. Sertoli-Leydig cell tumors of the ovary: A Taiwanese Gynecologic Oncology Group study. Taiwan J Obstet Gynecol 2013;52:66–70.
[7] Park JY, Jin KL, Kim DY, Kim JH, Kim YM, Kim KR, et al. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. Gynecol Oncol 2012;125:80–6.
[8] Thrall MM, Paley P, Pizer E, Garcia R, Goff BA. Patterns of spread and recurrence of sex cord-stromal tumors of the ovary. Gynecol Oncol 2011;122:242–5.
[9] Iyibozkurt AC, Topuz S, Gungor F, Akhan SE, Demirci F, Salihoglu Y, et al. Factors affecting recurrence and disease-free survival in granulosa cell tumors of the ovary. Eur J Gynaecol Oncol 2010;31:667–71.
[10] Ayhan A, Salman MC, Velipasaoglu M, Sakinci M, Yuce K. Prognostic factors in adult granulosa cell tumors of the ovary: A retrospective analysis of 80 cases. J Gynecol Oncol 2009;20:158–63.
[11] Hölscher G, Anthuber C, Bastert G, Burges A, Mayr D, Oberlechner E, et al. Improvement of survival in sex cord stromal tumors - An observational study with more than 25 years follow-up. Acta Obstet Gynecol Scand 2009;88:440–8.
[12] Auranen A, Sundström J, Ijäs J, Grénman S. Prognostic factors of ovarian granulosa cell tumor: A study of 35 patients and review of the literature. Int J Gynecol Cancer 2007;17:1011–8.
[13] Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary: An analysis of 376 women. Gynecol Oncol 2007;104:396–400.
[14] Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary-A multivariate analysis. Gynecol Oncol 2005;96:204–9.
[15] Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM. Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 1997;79:1951–5.
[16] Pautier P, Lhommé C, Culine S, Duvillard P, Michel G, Bidart JM, et al. Adult granulosa-cell tumor of the ovary: A retrospective study of 45 cases. Int J Gynecol Cancer 1997;7:58–65.
[17] Malmström H, Högberg T, Risberg B, Simonsen E. Granulosa cell tumors of the ovary: Prognostic factors and outcome. Gynecol Oncol 1994;52:50–5.
[18] Ohel G, Kaneti H, Schenker JG. Granulosa cell tumors in Israel: A study of 172 cases. Gynecol Oncol 1983;15:278–86.
[19] Mangili G, Ottolina J, Gadducci A, Giorda G, Breda E, Savarese A, et al. Long-term follow-up is crucial after treatment for granulosa cell tumours of the ovary. Br J Cancer 2013;109:29–34.
[20] Suri A, Carter EB, Horowitz N, Denslow S, Gehrig PA. Factors associated with an increased risk of recurrence in women with ovarian granulosa cell tumors. Gynecol Oncol 2013;131:321–4.
[21] Huang BS, Sun HD, Hsu YM, Chang WH, Horng HC, Yen MS, et al. Clinical presentation and outcome of adult-type granulosa cell tumors: A retrospective study of 30 patients in a single institute. J Chin Med Assoc 2014;77:21–5.
[22] Chua TC, Iyer NG, Soo KC. Prolonged survival following maximal cytoreductive effort for peritoneal metastases from recurrent granulosa cell tumor of the ovary. J Gynecol Oncol 2011;22:214–7.
[23] Fotopoulou C, Savvatis K, Braicu EI, Brink-Spalink V, Darb-Esfahani S, Lichtenegger W, et al. Adult granulosa cell tumors of the ovary: Tumor dissemination pattern at primary and recurrent situation, surgical outcome. Gynecol Oncol 2010;119:285–90.
[24] Madhuri TK, Butler-Manuel S, Karanjia N, Tailor A. Liver resection for metastases arising from recurrent granulosa cell tumour of the ovary–A case series. Eur J Gynaecol Oncol 2010;31:342–4.
[25] Tao X, Sood AK, Deavers MT, Schmeler KM, Nick AM, Coleman RL, et al. Anti-angiogenesis therapy with bevacizumab for patients with ovarian granulosa cell tumors. Gynecol Oncol 2009;114:431–6.
[26] Lee YK, Park NH, Kim JW, Song YS, Kang SB, Lee HP. Characteristics of recurrence in adult-type granulosa cell tumor. Int J Gynecol Cancer 2008;18:642–7.
[27] Uygun K, Aydiner A, Saip P, Kocak Z, Basaran M, Dincer M, et al. Clinical parameters and treatment results in recurrent granulosa cell tumor of the ovary. Gynecol Oncol 2003;88:400–3.
[28] Mangili G, Sigismondi C, Frigerio L, Candiani M, Savarese A, Giorda G, et al. Recurrent granulosa cell tumors (GCTs) of the ovary: A MITO-9 retrospective study. Gynecol Oncol 2013;130:38–42.
[29] Kampfrath T, Levinson SS. Brief critical review: Statistical assessment of biomarker performance. Clin Chim Acta 2013;19:102–7.
[30] Jamieson S, Fuller PJ. Molecular pathogenesis of granulosa cell tumors of the ovary. Endocr Rev 2012;33:109–44.
[31] Kanthan R, Senger JL, Kanthan S. The multifaceted granulosa cell tumours-myths and realities: a review. ISRN Obstet Gynecol 2012;2012:878635.
[32] Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cord-stromal tumors of the ovary: Can routine staging lymphadenectomy be omitted? Gynecol Oncol 2009;113:86–90.
[33] Gershenson DM, Morris M, Burke TW, Levenback C, Matthews CM, Wharton JT. Treatment of poor-prognosis sex cord-stromal tumors of the

ovary with the combination of bleomycin, etoposide, and cisplatin. Obstet Gynecol 1996;87:527–31.
[34] Homesley HD, Bundy BN, Hurteau JA, Roth LM. Bleomycin, etoposide, and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: A gynecologic oncology group study. Gynecol Oncol 1999;72:131–7.
[35] Pautier P, Gutierrez-Bonnaire M, Rey A, Sillet-Bach I, Chevreau C, Kerbrat P, et al. Combination of bleomycin, etoposide, and cisplatin for the treatment of advanced ovarian granulosa cell tumors. Int J Gynecol Cancer 2008;18: 446–52.
[36] Brown J, Shvartsman HS, Deavers MT, Ramondetta LM, Burke TW, Munsell MF, et al. The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors. Gynecol Oncol 2005;97:489–96.
[37] Wolf JK, Mullen J, Eifel PJ, Burke TW, Levenback C, Gershenson DM. Radiation treatment of advanced or recurrent granulosa cell tumor of the ovary. Gynecol Oncol 1999;73:35–41.
[38] Fishman A, Kudelka AP, Tresukosol D, Edwards CL, Freedman RS, Kaplan AL, et al. Leuprolide acetate for treating refractory or persistent ovarian granulosa cell tumor. J Reprod Med 1996;41:393–6.
[39] Freeman SA, Modesitt SC. Anastrozole therapy in recurrent ovarian adult granulosa cell tumors: A report of 2 cases. Gynecol Oncol 2006;103:755–8.
[40] Korach J, Perri T, Beiner M, Davidzon T, Fridman E, Ben-Baruch G. Promising effect of aromatase inhibitors on recurrent granulosa cell tumors. Int J Gynecol Cancer 2009;19:830–3.
[41] Gardia-Donas J, Hurtado A, García-Casado Z, Albareda J, López-Guerrero JA, Alemany I, et al. Cytochrome P17 inhibition with ketoconazole as treatment for advanced granulosa cell ovarian tumor. J Clin Oncol 2013;31:e165–6.